Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Long, relapsing, and atypical symptomatic course of COVID-19 in a B-cell-depleted patient after rituximab

Key message

Rituximab treatment was associated with prolonged SARS-CoV-2 infection and atypical symptoms in a GPA patient.

Sir, The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak poses uncertainties in patients with chronic inflammatory disease who develop coronavirus disease 2019 (COVID-19), as these patients are at risk because of their underlying disease and immunomodulatory/immunosuppressive therapies used for management. One of the agents used is rituximab, a B-cell-depleting agent.

Accumulating data from case series suggest that biological disease modifying anti-rheumatic drugs are not associated with worse COVID-19 outcomes and might even be protective [1,2]. However, extrapolation of these data to individual cases with potentially life-threatening manifestations or less common immunosuppressive agents could be dangerous. A higher risk for influenza-associated complications has been documented in immunosuppressed patients [3], and B cells play an essential role in the clearance of influenza [4], while the role of antibody-based immunity in COVID-19 infection has been questioned recently [5]. Therefore, the potential impact of rituximab on viral clearance remains unclear [6]. B-cell-depleting therapies could potentially alter COVID-19 infection rates, disease course, or outcomes. Individual cases provide important information on the course of COVID-19 infections in rare, potentially severe diseases.

We report the case of a 63-year-old man with COVID-19 under severe immunosuppression with rituximab (and previously cyclophosphamide). He was diagnosed six years earlier as myeloperoxidase (MPO)-positive granulomatosis with polyangiitis (GPA) with the following manifestations: severe pauci-immune glomerulonephritis, sensory neuropathy, and sinusitis. Initially he received a combination of cyclophosphamide, rituximab and methylprednisolone (RITUXVAS protocol) as well as several plasma exchanges. Maintenance therapy consisted of 5 mg prednisolone and 500 mg rituximab; the most recent administration was two weeks before the onset of COVID symptoms. Medications for comorbidities consisted of candesartan, amlodipine, and torasemide for hypertension and amitriptyline and pregabalin for sensory neuropathy.

The patient was admitted to the hospital with dry cough, sore throat, and lack of appetite for 2 days (further symptoms such as fever, diarrhea, or loss of taste/smell were denied). Computed tomography (CT) scan revealed ground-glass opacities in segments 6 and 9 of the left lower lobe suggestive of COVID-19, and a positive nasopharyngeal swab confirmed the SARS-CoV-2 diagnosis. Initial laboratory tests showed normal differential blood count and C-reactive protein (CRP) levels, as well as normal levels for other COVID-19 markers (D-dimer, ferritin and lactic acid dehydrogenase). Creatinine levels were elevated (2.24 mg/dL), but stable compared with recent values. Immunophenotyping revealed depletion of $CD19^+$ B cells and normal CD3 T cell and NK cell counts. Neutrophil and macrophage function were normal. Consistent with long-term B cell depletion, IgG and IgM levels were low (4.07 and 0.12 g/L, respectively). Despite mild symptoms, the patient was hospitalized for clinical monitoring due to his risk profile. During this hospital stay the patient required low-flow oxygen therapy by nasal canula (peripheral oxygen saturation <90%) for three days, CRP increased slightly to 12.5 mg/L, and he remained afebrile and clinically stable. The patient was discharged to domestic quarantine on day 12.

Two days later the patient was re-admitted due to fatigue and lack of appetite; SARS-CoV2 remained detectable in the nasopharyngeal swab. A CT scan showed progressive, bilateral ground-glass opacities although the patient still had only minimal respiratory symptoms. CRP levels were elevated at 37.1 mg/L and peaked at day 11 (104 mg/L) of the hospital stay. Serum creatinine increased from 2.24 to 3.4 mg/dL, probably related to the infection, as relapse of glomerulonephritis was unlikely given the negative urine sediment and negative MPO-anti-neutrophil cytoplasmic autoantibody status. Starting from day 20, the patient needed constant respiratory support with up to 6 liters of oxygen via face mask. After day 28 the patient improved, and oxygen therapy was stopped at day 30. Sputum test became negative for COVID-19 32 days after the start of symptoms and the patient was discharged home.

This case brings attention to the potential for late disease development in rituximab-treated patients infected with SARS-CoV-2. Our initial findings of mild symptoms with normal CRP are in line with the mild course of COVID-19 in another GPA patient under rituximab and the same observation in patients with agammaglobulinemia patients [7]. However, in contrast to previous case reports [7,8], our patient relapsed shortly after discharge leading to a second admission with atypical symptoms (fatigue, lack of appetite) and, ultimately, severe respiratory distress. This disease course suggests that rituximab-treated patients can experience worsening of infection after initial resolution of symptoms and may present with atypical symptoms.

It is possible that B cell depletion prevents a cytokine storm, thereby resulting in a milder disease course. However, at the same time, the reduced B cell levels may result in reduced viral clearance, despite normal T cell and normal neutrophil counts and function. In the case reported here, the patient remained SARS-CoV2 positive for more than 30 days after initial symptoms, highlighting the importance of B-cell function and antibody derived-immunity in resolving this viral infection. Furthermore, it shows that patients on B-cell-depleting therapies may shed virus for a prolonged period while remaining asymptomatic, thereby possibly endangering other individuals.

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Declaration of Competing Interest

The authors declare no conflict of interest

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